Amendments to the Claims

This listing of claims replaces all prior versions and listings of claims in the application.

Listing of Claims

1-75. (Canceled)

76. (New) A Factor VII or Factor VIIa polypeptide comprising a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native Factor VII or Factor VIIa polypeptide, said modified GLA domain comprising at least one amino acid substitution at position 33, 34, or 35, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3.

77. The polypeptide of claim 76, wherein a hydrophobic amino acid residue is substituted at position 33.

78. The polypeptide of claim 77, wherein a phenylalanine, leucine or isoleucine residue is substituted at position 33.

79. The polypeptide of claim 76, wherein a hydrophobic amino acid residue is substituted at position 34.

80. The polypeptide of claim 79, wherein a phenylalanine, leucine or isoleucine residue is substituted at position 34.

81. The polypeptide of claim 76, wherein an aspartic acid or glutamic acid residue is substituted at position 34.

82. The polypeptide of claim 81, wherein a glutamic acid residue is substituted at position 34.

83. The polypeptide of claim 76, wherein a hydrophobic amino acid residue is substituted at position 35.

84. The polypeptide of claim 84, wherein a phenylalanine, leucine or isoleucine residue is substituted at position 35.

85. The polypeptide of claim 76, further comprising an amino acid substitution at position 10 or 11.

86. The polypeptide of claim 85, wherein a glutamine, asparagine, glutamic acid, or aspartic acid residue is substituted at position 10.

87. The polypeptide of claim 86, wherein a glutamine residue is substituted at position 10.

88. The polypeptide of claim 76, further comprising an amino acid substitution at position 32.

89. The polypeptide of claim 88, wherein a glutamic acid residue is substituted at position 32.

90. The polypeptide of claim 76, further comprising an amino acid substitution at position 28.

91. The polypeptide of claim 90, wherein a phenylalanine or a glutamic acid residue is substituted at position 28.

92. The polypeptide of claim 91, wherein a phenylalanine residue is substituted at position 28.

93. The polypeptide of claim 76, further comprising an insertion at position 4.

94. The polypeptide of claim 93, wherein a tyrosine or glycine residue is inserted at position 4.

95. The polypeptide of claim 94, wherein a tyrosine residue is inserted at position 4.

96. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a Factor VII or Factor VIIa polypeptide, wherein said Factor VII or Factor VIIa polypeptide comprises a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native Factor VII or Factor VIIa polypeptide, said modified GLA domain comprising at least one amino acid substitution at position 33, 34, or 35, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3.

97. The pharmaceutical composition of claim 96, wherein the Factor VII or Factor VIIa polypeptide further comprises a glutamine residue substituted at position 10 and a glutamic acid residue substituted at position 32.

98. A mammalian host cell that expresses a Factor VII or Factor VIIa polypeptide, said Factor VII or Factor VIIa polypeptide comprising a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native Factor VII or Factor VIIa polypeptide, said modified GLA domain comprising at least one amino acid substitution at position 33, 34, or 35, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3.

99. A method of increasing clot formation in a mammal comprising administering an amount of a Factor VII or Factor VIIa polypeptide effective to increase clot formation in said mammal, wherein said Factor VII or Factor VIIa polypeptide comprises a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native Factor VII or Factor VIIa polypeptide, said modified GLA domain comprising at least one amino acid substitution at position 33, 34, or 35, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3.

100. A method for treating a bleeding disorder in a patient, said method comprising administering the pharmaceutical composition of claim 96 to said patient.

101. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding the polypeptide of claim 76.

102. A method for producing a Factor VII or Factor VIIa polypeptide having a modified GLA domain comprising at least one amino acid substitution at position 33, 34, or 35, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3, the method comprising (a) providing a culture of the mammalian host cell of claim 98 under conditions which permit expression of the polypeptide, and (b) recovering the polypeptide.

103. A modified Factor VII or Factor VIIa polypeptide, comprising an insertion at position 4, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3.

104. The polypeptide of claim 103, wherein a tyrosine or glycine residue is inserted at position 4.

105. The polypeptide of claim 104, wherein a tyrosine residue is inserted at position 4.

106. The polypeptide of claim 105, further comprising a modified GLA domain comprising at least one amino acid substitution at position 33, 34, or 35.

107. The polypeptide of claim 106, wherein said at least one amino acid substitution is selected from the group consisting of:

a) a phenylalanine, leucine or isoleucine residue at position 33;

b) a phenylalanine, leucine, isoleucine, aspartic acid or glutamic acid residue at position 34; and

c) a phenylalanine, leucine or isoleucine residue at position 35.

108. The polypeptide of claim 107, further comprising at least one amino acid substitution at position 10, 11, 28, or 32.

109. The polypeptide of claim 108, comprising at least one amino acid substitution selected from the group consisting of:

a) a glutamine, asparagine, glutamic acid, or aspartic acid residue at position 10;

b) a phenylalanine or glutamic acid residue at position 28; and

c) a glutamic acid residue at position 32.

110. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a modified Factor VII or Factor VIIa polypeptide comprising an insertion at position 4, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3.

111. A mammalian host cell that expresses a modified Factor VII or Factor VIIa polypeptide comprising an insertion at position 4, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3.

112. A method of increasing clot formation in a mammal comprising administering an amount of a modified Factor VII or Factor VIIa polypeptide effective to increase clot formation in said mammal, wherein said modified Factor VII or Factor VIIa polypeptide comprises an insertion at position 4, and wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3.

113. A method for treating a bleeding disorder in a patient, said method comprising administering the pharmaceutical composition of claim 110 to said patient.

114. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding the polypeptide of claim 103.

115. A method for producing a modified Factor VII or Factor VIIa polypeptide comprising an insertion at position 4, wherein amino acid positions of the Factor VII or Factor VIIa polypeptide are numbered according to SEQ ID NO:3, the method comprising (a) providing a culture of the mammalian host cell of claim 111 under conditions which permit expression of the polypeptide, and (b) recovering the polypeptide.